REMARKS

The Official Action dated January 18, 2007 and references cited therein have been carefully reviewed. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Status of the prosecution.

This reply is submitted together with a Request for Continued Examination pursuant to 37 C.F.R. §1.114.

A final rejection of claims 163-174 was issued in the January 18, 2007 Office Action. All claims remain rejected on the grounds of nonstatutory double patenting as allegedly unpatentable over claims 1-34 of U.S. Patent 7,045,145. The Action acknowledged Applicant's intention to file a terminal disclaimer upon determination of allowable subject matter.

Claims 163-166 and 171-174 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. 5,762,956 (the 956 patent) in view of U.S. 5,023,084 (the 084 patent).

Claims 167-170 remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the 956 patent in view of the 084 patent, and further in view of U.S. 6,007,835 (the 835 patent).

Current amendments to the specification and claims.

The specification has been amended to provide updated information pertaining to related applications. The pending claims have not been amended. New claim 175 has been added. Claim 175 depends from claim 173 and recites a functional limitation of delivery *in vivo* of an average serum concentration of over 1,000 pg/ml of levonorgestrel when the system is applied to human skin once each week over a period of three or more weeks. No new matter has been added. For the reasons set forth below, Applicant submits that the claims are in condition for allowance.

The claimed subject matter is not obvious in view of the cited prior art.

Claims 163-166 and 171-174 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. 5,762,956 (the 956 patent) in view of U.S. 5,023,084 (the 084 patent). Claims 167-170 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the 956 patent in view of the 084 patent, and further in view of U.S. 6,007,835 (the 835 patent). According to the Office Action, the 084 patent teaches a transdermal estrogen/progesterone dosage unit comprising an adhesive matrix with permeation enhancers, wherein capric acid is a preferred enhancing agent because it provides "highly satisfactory skin absorption enhancement." The Office Action alleges that, for this reason, the skilled artisan would have been motivated to modify the three-enhancer-containing transdermal delivery device taught by the 956 patent by the addition of capric acid as a fourth skin permeation enhancer, with a reasonable expectation of having a transdermal delivery device with highly satisfactory skin absorption enhancement for the combination of estrogen and progesterone. Applicant respectfully traverses these rejections for several reasons.

First, it must again be emphasized that the art of transdermal hormone delivery is unpredictable. Substantial evidence on this point has been presented in the declaration of Dr. Agis Kydonieus, with numerous supporting scientific references, submitted in response to the first Office Action in this application. The Kydonieus declaration sets forth a detailed explanation as to why transdermal hormone delivery is unpredictable, even when enhancers are not used (Kydonieus Decl. ¶¶10-13). When chemical enhancers are employed, the complexity and unpredictability of transdermal systems increase because they behave substantially differently when co-delivered with other enhancers and with the drugs themselves (Kydonieus Decl. ¶¶14-16). For these reasons the effect of enhancers on the permeation of drugs through skin is unpredictable and dependent on many variables whose effect can only be determined by experimentation (Kydonieus Decl., ¶17).

Notably, the unpredictability of the art of transdermal delivery is also taught in the 084 patent itself, which states at column 17, lines 15-24:

> The skin permeation enhancers which can be used in carrying out this invention can vary. Ones that give preferred results with the polymer dosage unit form having a specific hormone can vary. In some instances, the use of permeation enhancer in making a dosage unit will result in good or even excellent absorption for one hormone, may result in no or relatively low enhancement when another hormone is used.

The 084 patent teaches a transdermal progestin/estrogen delivery system that differs significantly from the system claimed in the present invention. Unlike the presently claimed system that utilizes an adhesive polymer matrix in which the hormones and enhancers are dispersed *together*, the 084 patent's system comprises multiple layers in which the estrogen is dispersed in a layer *separate* from the progestin and the skin permeation enhancer.

The Supreme Court has recently reiterated standards for determining obviousness of an invention composed of several elements, and has stated:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent applications that claims as innovation the combination of two or more devices according to their established functions, in can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in a way that the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR International Co. v. Teleflex Inc., 550 U.S. ____ [No. 04-1350], 2007.

In view of (1) the unpredictability of the relevant art, and (2) the differences between the transdermal system of the 084 patent and that of the 956 patent, there would have been no reason for one of skill in the art to combine the elements of the 084 patent with that of the 956 patent to arrive at the invention as presently claimed. In part, this is because the unpredictable nature of the art would not allow the skilled artisan to infer an established function for any of the skin permeation enhancers taught by the 084 patent, so as to impart any reasonable belief that any of those compounds would be useful in a dissimilar transdermal delivery system, such as the system of the present invention.

Second, the 084 patent and the 956 patent teach away from the claimed invention. In particular, the 956 patent teaches away from adding *anything* to the enhancer combination disclosed therein. As acknowledged by the Office Action, the 956 patent teaches a progestin/estrogen transdermal delivery device that utilizes a combination of three skin permeation enhancers. Importantly though, through its repeated use of the term "consisting of," the 956 patent teaches that its three enhancer system is not amenable to alteration or supplementation (see claim 1, for example, directed to a TCDS that contains "a combination

of skin permeation enhancing agents which is a mixture *consisting of* dimethyl sulfoxide, a fatty (C_8-C_{20}) alcohol ester of lactic acid and a lower (C_1 –C_4) alkyl ester of lactic acid present in an about 2.5-5:1:1 ratio" (emphasis added)). The 956 patent further discloses that the skin permeation enhancers "consist of" a "unique combination," as highlighted by the following passage (column 3, lines 23-37):

> The skin permeation enhancers utilized in the present invention *consist of* a combination of dimethyl sulfoxide (DMSO), a fatty alcohol ester of lactic acid and lower (C_1-C_4) alkyl ester of lactic acid. . . . . Applicants have made the surprising discovery that the *unique combination* of skin permeation enhancers utilized in the present invention, when homogeneously dispersed in the adhesive polymer matrix at a particular ratio (preferably, 2.5-5:1:1, respectively), acts to solubilize the dispersed estrogen and progestin, thus greatly enhancing the skin permeation of the steroid hormones contained in the TCDS (*emphasis added*).

It should be noted that two of the three inventors on the 956 patent were also inventors on the earlier-filed 084 patent. Despite this, the 956 patent makes no mention of any possibility of adding capric acid into its "unique combination" of skin permeation enhancers. To the contrary, by its language, the 956 patent actually *excludes* the presence of any other enhancer, capric acid or otherwise. Surely, if it was obvious that addition of capric acid to the permeation enhancer composition disclosed in the 956 patent would further enhance transdermal hormone delivery, or at the very least not be detrimental, the inventors of the 084 patent would have included such a possibility in the 956 patent, or at the very least not excluded the possibility.

Thus, the 956 patent's teachings actually lead the skilled artisan away from modifying the 956 patent's system in the manner claimed in the present application. As was again noted recently by the U.S. Supreme Court, "when the prior art teaches away from combining certain known elements, discovering a successful means of combining them is more likely to be nonobvious." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ____ [No. 04-1350], 2007 (citing *United States v Adams*, 383 U.S. 39, 51-52, 1966). Such is the case in the instant application.

Furthermore, with respect to the specific subject matter of claim 173, the 084 patent also teaches away from the notion of incorporating capric acid into an adhesive polymer matrix system for delivery of levonorgestrel. Though the 084 patent describes capric acid

and n-decyl alcohol as "preferred enhancing agents" in general, the ability of capric acid to enhance delivery of levonorgestrel is *not* taught in the 084 patent and, in fact, is particularly omitted (column 18, lines 32-39).

> A combination of 20 parts of either alpha-tocopherol, retinol, retinyl palmitate, retinoic acid, dl-alpha-tocopherol, dl-alpha tocopherol acetate, or combinations thereof together with 100 parts of n-decyl alcohol have been found to be effective enhancing agents in carrying out the invention, such as for example when levonorgestrel or norgestrel or biocompatible derivatives thereof are used as the progestin.

In addition, with the exception of Example 10 and Table 16, all *in vitro* data showing the effect of enhancers on hormone delivery are with norethindrone, not levonorgestrel. Example 8 of the 084 patent describes the effect of enhancers on delivery of levonorgestrel, but those enhancers were n-decyl alcohol alone or combined with secondary enhancers as listed above, and *not* capric acid. Thus, the skilled artisan reviewing the information set forth in the 084 patent would have no reason to select capric acid to add to the three enhancer system of the 956 patent for delivery of levonorgestrel.

Finally, referring particularly to new claim 175, Applicant further notes that the 956 patent teaches that its three-enhancer system delivers levonorgestrel sufficient only to achieve an average serum concentration of 300-400 pg/ml when worn on the skin for a three-week period (956 patent, Fig. 4). Thus, in addition to failing to teach a four-component enhancer system, the 956 patent fails to teach the additional functional limitation recited in claim 175.

The 084 patent is silent with respect to *in vivo* serum concentrations of the hormones sought to be delivered by its disclosed device. Accordingly, the reference certainly cannot be said to provide any explicit teaching concerning *in vivo* efficacy for delivery of levonorgestrel, as claimed in claim 175.

Hence, there is no rational basis taken from either the 084 or the 956 patent to think that any skilled artisan would believe that addition of capric acid to the system of the 956 patent would result in any change whatsoever, positive or negative, in transdermal delivery of levonorgestrel as claimed in claim 173, and certainly none to believe that such a modification would result in an average *in vivo* serum concentration of greater than 1000 pg/ml levonorgestrel, as claimed in claim 175.

The addition of the 835 patent to support the rejection of claims 167-170 is also untenable in view of the absence of teaching in the 956 patent and the 084 patent of the

invention as currently claimed. The 835 patent's purported teaching of PVP/VA-S30 do not supply a reason to combine the teachings of the cited references so notably absent from the primary references.

In summary, Applicant has presented reasoning and evidence to support his assertion that the invention as presently claimed is not obvious over the cited references. In view of the general unpredictability of transdermal drug delivery, one seeking to improve on the transdermal system of the 956 patent would not have found sufficient information in any of the cited references, alone or in combination, to make the specific modifications claimed in the present application, to arrive at the claimed transdermal delivery system. Applicant therefore requests reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

Conclusion.

In view of the amendments submitted herewith and the foregoing remarks, the presently pending claims are believed to be in condition for allowance. Applicant respectfully requests early and favorable reconsideration and withdrawal of the rejections set forth in the January 18, 2007 Official Action, and allowance of this application.

Respectfully submitted,

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